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Albumin as a Carrier in Nanodrug Delivery System: A Review

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ABSTRACT

The utilization of albumin nanoparticles as a potent nanodrug carrier has shown considerable promise in modern therapeutic approaches. Human serum albumin serves as an efficient nano-drug carrier for a diverse range of disorders, demonstrating its versatility in medical applications. This multifaceted protein has been employed in the treatment of various disorders, showcasing its potential across a spectrum of medical conditions. The preparation of albumin nanoparticles involves a methodical process, where human serum albumin is structured into nanoparticles, contributing to its role in delivering and enhancing drug therapies. The abstract summarizes the significant role of albumin nanoparticles as a drug carrier, emphasizing the use of human serum albumin in diverse disorder treatments and highlighting the systematic preparation of albumin nanoparticles, underscoring their importance in modern therapeutic interventions. The significance of albumin as a delivery system for hydrophobic medications is examined in this study, which makes use of both passive and active targeting mechanisms. With an emphasis on the benefits of Nab-Paclitaxel (Abraxane) over solvent-based Paclitaxel formulations like CrEL-paclitaxel (Taxol) in clinical settings, it particularly highlights the cutting-edge technology. The article also describes current clinical trials employing albumin-based formulations and highlights the important function that albumin plays in transporting anticancer drugs. It highlights the importance of the carrier in improving medication performance inside biological systems and highlights the possibility of using albumin as a drug delivery mechanism. The article makes a few suggestions about possible developments in the use of this medication delivery method in the future.

INTRODUCTION:

Nanotechnology has shown significant promise in medical applications, especially in delivering medications. (1) Specifically, nanomaterial have enabled the development of systems for effective transport, protection, and precise delivery of complex therapeutic or diagnostic substances in biological fluids. These materials are capable of targeting cellular and intracellular locations, including poorly soluble drugs, proteins, and gene therapies. (2)

The natural protein albumin, present in blood plasma, has garnered attention from researchers as a versatile nano delivery system. It possesses unique characteristics that make it an attractive option, such as a high capacity to bind both hydrophobic and hydrophilic drugs, an extended lifespan in the body, precise targeting of inflammation sites, and minimal toxicity or potential for causing an immune response. (3)

Albumin, an essential plasma protein, has become prominent in the realm of nanodrug delivery systems due to its exceptional biocompatibility and degradability, providing a solid foundation for delivering medications. (4)

Utilizing albumin nanoparticles or drugs bound to albumin offers multiple benefits as a carrier. These methods can enhance drug solubility, prolong the time drugs circulate in the body, and improve the targeting of medications to specific tissues. Moreover, albumin nanoparticles can be tailored to accommodate a broad spectrum of therapeutic compounds, including chemotherapy drugs and imaging agents, thus establishing them as a versatile tool in the field of nanomedicine .(5)

Furthermore, the outer surface of albumin-based nanoparticles can be customized with ligands by utilizing the functional groups available for attaching various linkers or spacers. These nanoparticles have the potential to engage in active targeting without the need for external ligands, as they can be recognized by gp60 receptors and secreted proteins, particularly those rich in cysteine, such as SPARC. Numerous comprehensive reviews have been published on albumin nanoparticles, highlighting their significance in research and applications. (53)

Albumin:

Albumin, a protein found in various sources such as egg white (ovalbumin), bovine serum albumin (BSA), and human serum albumin (HSA), plays a crucial role in the body's soluble protein system. (6) It helps regulate osmotic pressure and is essential for binding and

transporting nutrients to cells. Numerous drugs and natural compounds are known to bind with albumin.

Acting as both a reservoir and a transporter, albumin is highly soluble in water and diluted salt solutions.(6) Its exceptional solubility at pH 7.4, reaching concentrations of up to 40% w/v, makes it an attractive macromolecular carrier suitable for a wide range of drugs. It maintains stability within the pH range of 4 to 9 and can endure heating at 60°C for up to 10 hours without adverse effects.(7)

In the field of nanotechnology, albumin is extensively utilized in the production of nanospheres and nano capsules.(8) These albumin-based nano-carriers are biodegradable, easy to prepare, and have precisely defined sizes and surface reactive functional groups such as thiol, amino, and carboxyl, allowing for ligand binding and surface modifications. The release of drugs from albumin nanoparticles can occur naturally through protease digestion. (8)

Basic functions of Albumin:

Albumin serves a crucial role as a carrier protein within the bloodstream, facilitating the transport and stabilization of various essential compounds, including steroids, fatty acids, and thyroid hormones. In particular, it functions to solubilize long-chain fatty acids, playing a pivotal role in lipid metabolism. Additionally, it binds bilirubin, a breakdown product of heme, and interacts with a wide array of therapeutic drugs such as penicillins, sulfonamides, indole compounds, and benzodiazepines.

This versatile protein also exhibits specific binding characteristics towards certain metal ions like copper (II) and nickel (II), while displaying a relatively nonspecific binding pattern for calcium(II) and zinc(II). It serves as the primary transport vehicle for these metal ions in the bloodstream and is pivotal in maintaining the blood's colloid osmotic pressure.

Furthermore, the breakdown of HSA provides essential amino acids, offering nutrition to peripheral tissues. Notably, the required levels of albumin may vary in smaller animals, like rats, as they operate at lower blood pressures, necessitating less oncotic pressure for proper fluid distribution. [6]

Albumin is a blood protein that has numerous significant features and functions:

- Protein structure: Albumin is a globular protein that has a molecular weight of around 66.5 kDa. It is made up of 585 amino acid residues in a single polypeptide chain. The protein's three-dimensional structure is well defined.

- Solubility: Albumin is extremely soluble in water and is essential in controlling blood osmotic pressure, preventing excessive fluid from seeping out of blood vessels into surrounding tissues.

- Transport Protein: Albumin is a carrier protein that binds to a variety of chemicals in the blood, including hormones, fatty acids, medicines, and numerous tiny molecules. This transport function aids in the distribution of these chemicals throughout the body.

- Buffering Capacity: Albumin has buffering capacity, which means it can help keep blood pH within a relatively narrow range, thereby contributing to acid-base balance in the body.

- Osmotic Pressure Regulation: Osmotic Pressure Regulation: Albumin is in charge of keeping blood's colloidal osmotic pressure, also known as oncotic pressure, stable. This pressure aids in the retention of fluid within the blood vessels and prevents excessive fluid leakage into tissues.

- Nutrient Reservoir: Albumin acts as a nutrient reservoir, storing nutrients such as fatty acids that can be released as needed to provide energy.

- Antioxidant Properties: Albumin has some antioxidant properties that can help to protect cells and tissues from oxidative damage.

- Liver Synthesis: The liver is the primary site of albumin synthesis. As a result, measuring albumin levels in the blood can be used as an indicator of liver function.

- Half-Life: Albumin has a relatively long half-life in the bloodstream, around 20 days, which contributes to its stability and long-lasting effects in the body.

- Diagnostic Marker: Albumin levels in the blood that are abnormal can be indicative of a variety of health conditions. Low albumin levels (hypoalbuminemia) are common in conditions such as liver disease, malnutrition, and kidney disease, whereas high albumin levels are less common but may indicate dehydration or certain rare conditions.(6)

Special feature of albumin as a drug carrier:

Renowned for its exceptional ligand-binding capacity, albumin is an adaptable protein with multifaceted roles encompassing antioxidant, immunomodulatory, detoxifying, and potent drug-carrying capabilities. (14) Its diverse applications span both exogenous and endogenous treatments for various conditions, including hepatitis, diabetes, rheumatoid arthritis, and cancer. Utilizing albumin as a foundation, drug delivery systems have taken the form of albumin-drug nanoparticles, fusion proteins, pro-drugs, and peptide derivatives that attach to antibody fragments and therapeutically active peptides.

A focal point of debate over the past decade has been the efficacy of albumin as a superior drug carrier for delivering macromolecules. Notably, human serum albumin (HSA) exhibits a wide binding capacity, encompassing a remarkably broad spectrum of compounds, often at concentrations surpassing their bioavailability in plasma. This binding ability is facilitated by HSA's negative charge, enabling electrostatic bonding with diverse ligands, and functioning as a repository and carrier for a multitude of medicinal substances.

The distinctive characteristics that define albumin as an exceptional drug carrier include its role as a transporter, facilitated by the binding sites within its tertiary structure. The diverse array of materials transported by albumin ranges from drugs, bilirubin, hormones, and metals to anions, fatty acids, and bacterial products like the protein G-like albumin-binding molecule. The variety of molecules that can bind to albumin mirrors the multiple binding mechanisms involving covalent binding, hydrophobic and electrostatic interactions, and complex formation with metals.

Moreover, albumin's multiple binding sites contribute to its versatility in accommodating various ligands, each displaying unique methods, selectivities, and binding capabilities to albumin. Albumin's remarkable adaptability renders it a pivotal component in drug delivery systems. Notably, seven binding sites have been identified for fatty acids, with the most significant sites for drug binding situated at sites I and II on sub-domains IIA and IIIA, respectively. Complex formation and high-affinity binding typically take place in either a reversible or irreversible manner, contributing significantly to albumin's role as a carrier in drug delivery. (15)

Albumin nanoparticles:

Nanoparticles have gained considerable attention as carriers for medications. They enhance the solubility and precision targeting of therapeutic compounds with low bioavailability and toxic limitations, offering significant advantages. However, recent research indicates that nanoparticles larger than 100 nm often struggle to enter into diseased areas or tumor microenvironments (TMEs). Their variable bio-distribution and inter tumoral variance limit their penetration, particularly within solid tumors.

To address the limitations of traditional nanomedicines, albumin-based nanoparticles present compelling solutions. Albumin, with its multiple intrinsic drug-binding sites, easily accommodates numerous hydrophobic compounds. Additionally, targeted receptors or drugs can be linked to albumin's inherent functional groups, such as charged amino acids and carboxylic and amino moieties, using cleavable linkers for controlled release. Moreover, as mentioned earlier, albumin's ability to actively bind to tumors and inflammatory sites enhances the effective penetration of albumin-based nanoparticles.

PREPARATION METHODS OF ALBUMIN:

Albumin-based nanoparticles can be generated using various manufacturing methods, broadly classified into chemical-based and physical-based techniques. Chemical-based approaches involve the use of additives like ethanol, cottonseed oil, or β-mercaptoethanol, employing methods such as self-assembly, emulsification, and desolation. Physical-based methods, on the other hand, rely on physical elements such as heat or pressure and encompass techniques like thermal gelation, NAB-technology, and nanospray drying. It's crucial for each manufacturing process to aim for consistent reproducibility, ensuring the creation of nanoparticles with predictable and repeatable characteristics. (16)

1. Desolvation: The desolvation method stands out as a popular technique for producing albumin nanoparticles. This process involves a gradual and continuous addition of a desolvating substance, such as ethanol or acetone, to an aqueous solution of albumin while maintaining agitation until the solution turns cloudy. (16) The introduction of desolvating agents induces phase separation and prompts protein aggregation by gradually modifying the albumin's tertiary structure. Consequently, the initially homogeneous solution separates into two phases: the albumin, forming submicronic aggregates, and the solvent, which primarily constitutes the second phase. However, the resulting formulation is often insufficiently stable, necessitating the use of a crosslinker, such as glutaraldehyde, to further preserve and stabilize

the shape of the resulting nanoparticles. Various process parameters, including pH, protein content, cross-linker concentration, desolvating agent level, ionic strength, and stirring speed, significantly influence the ultimate qualities of the formulated nanoparticles. (17) The preparation process is shown figure 3A.

2. Emulsification: An oil-based solution is introduced to an albumin water solution to create a basic emulsion, which is agitated. This mixture can then be processed through a high-pressure homogenizer to attain consistency. Afterward, the nanoparticles can be stabilized by either utilizing a cross-linker such as glutaraldehyde through chemical treatment or by subjecting them to a high temperature exceeding 120°C. (19)

3. Self-Assembly method : The creation of albumin nanoparticles through self-assembly relies on altering the protein's properties. This modification occurs by making the protein more hydrophobic, either by breaking down disulfide bonds using β-mercaptoethanol or reducing the number of primary amine groups on the protein's surface with a lipophilic compound. Consequently, in an aqueous environment, albumin begins to self-assemble, leading to the formation of nanoparticles. The process is depicted in Figure 3C.

4. Thermal Gelation: Thermal gelation, as shown in Figure 3D, involves a change in protein structure and unfolding due to heat. Subsequently, proteins interact, forming hydrogen bonds, electrostatic forces, hydrophobic interactions, and reactions between disulfide and sulfhydryl groups. The properties of the resulting formulation are affected by process variables like pH, protein concentration, and ionic strength. (21)

5. Drying with Nanospray: Nanospray drying, depicted in Figure 3E, is a widely used technique to convert a liquid phase into dry powder, offering flexibility in its application. One of its key benefits is its ability to produce particles in a continuous, single stage. The process begins with the formation of droplets from a liquid solution by spraying. Several steps are involved, including atomizing the feed into a spray, mixing it with air, drying the spray, and then separating the dried product from the drying air. During this process, the liquid feedstock forms a spray of droplets upon contact with a drying gas at a sufficiently high temperature to facilitate moisture evaporation. (24) This interaction occurs within a drying chamber containing an aqueous albumin solution.(25)

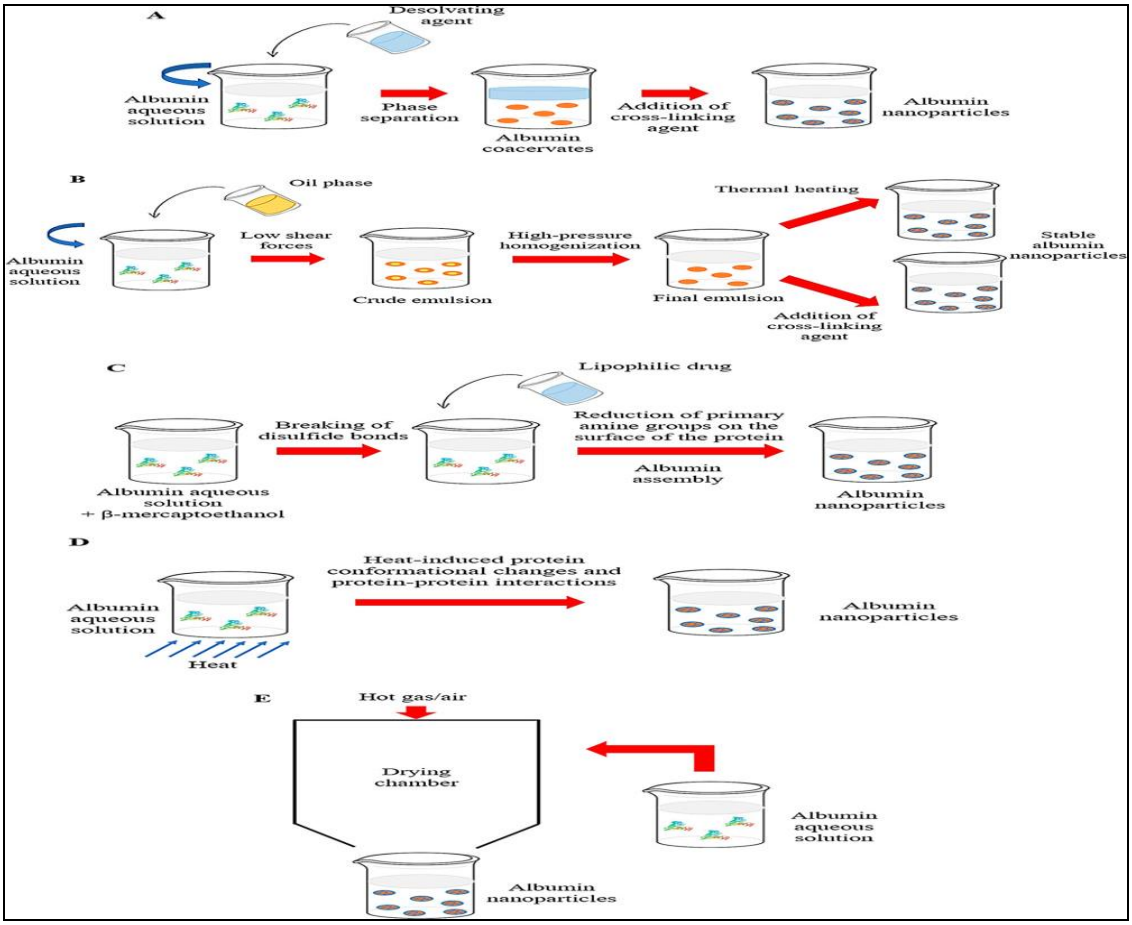

Fig. 1. Methods for the preparation of albumin nanoparticles: (1) Desolvation, (2) Emulsification, (3) Self-assembly, (4) Thermal gelation, (5) Drying with Nanospray

Microfluidic mixing: A different method for creating albumin nanoparticles is microfluidic technology, albeit one that has received less research.(26) Lipid, polymeric, and serum albumin nanoparticles can be effectively made using it as a substitute. Particles with a narrow size distribution and tunable size are produced by this technique, which is a controlled preparation process. Moreover, it offers a special chance for large-scale, automated pharmaceutical manufacturing. The synthesis of albumin nanoparticles underflow conditions has not been extensively studied in the literature. (27) A study carried out in 202075 that concentrated on the preparation of drug-loaded albumin-based nanoparticles with a core-shell structure produced successful outcomes. In the first syringe pump, channel 1 (v1) was filled with the stabilizer poly (allylamine hydrochloride) (PAH), and channel 2 (v2) was filled with the drug and carrier solution (BSA/KYNA). (28) Following the syringe pumps, the two solutions were combined in a 250 µL µ-mixer cell with a pressure controller device. Subsequently, the sample was taken at predetermined intervals. Figure 4 shows a schematic representation of how this microfluidic device prepares the core-shell nanoparticles

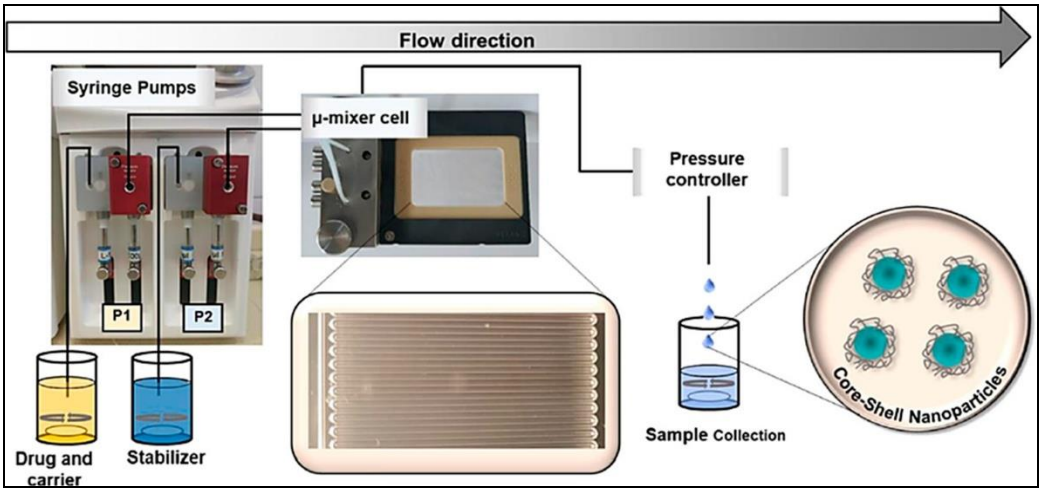

Fig. 2 . Flow system used to prepare core-shell nanoparticles.(29)

Human Serum Albumin:

Human serum albumin (HSA) makes up over half of the total protein in humans, making it the most abundant protein in plasma (9-10). 75%–80% of plasma's problems are primarily caused by albumin. Normal is the colloid oncotic pressure. It can carry nutrients to cells, solubilize long-chain fatty acids, and balance the pH of plasma. Serum albumin is spontaneously produced by the liver. Incorporated into blood plasma. Inadequate or excessive There could be negative effects from serum albumin circulation (10). It might be a vital carrier that improves the pharmacokinetic characteristics of small compounds. Among the drug compounds are peptides and protein-based medications.

Approximately 66.5 kDa is the molecular weight of albumin. HSA is used to treat shock, burns, hypoalbuminemia, surgery or trauma, cardiac bypass, acute respiratory distress, and hemodialysis. Albumin, like most plasma proteins, is generated in the liver at a rate of roughly 0.7 mg/h for every gram of liver (i.e., 10-15 g daily). Blood-derived albumin can now be substituted by recombinant human serum albumin, or recombumin. The protein, which is genetically modified and produced in yeast cells, has demonstrated properties similar to native HAS in terms of safety, tolerability, pharmacokinetics, and pharmacodynamics (10). HSA is being utilized more and more as a medication carrier in the clinical context.

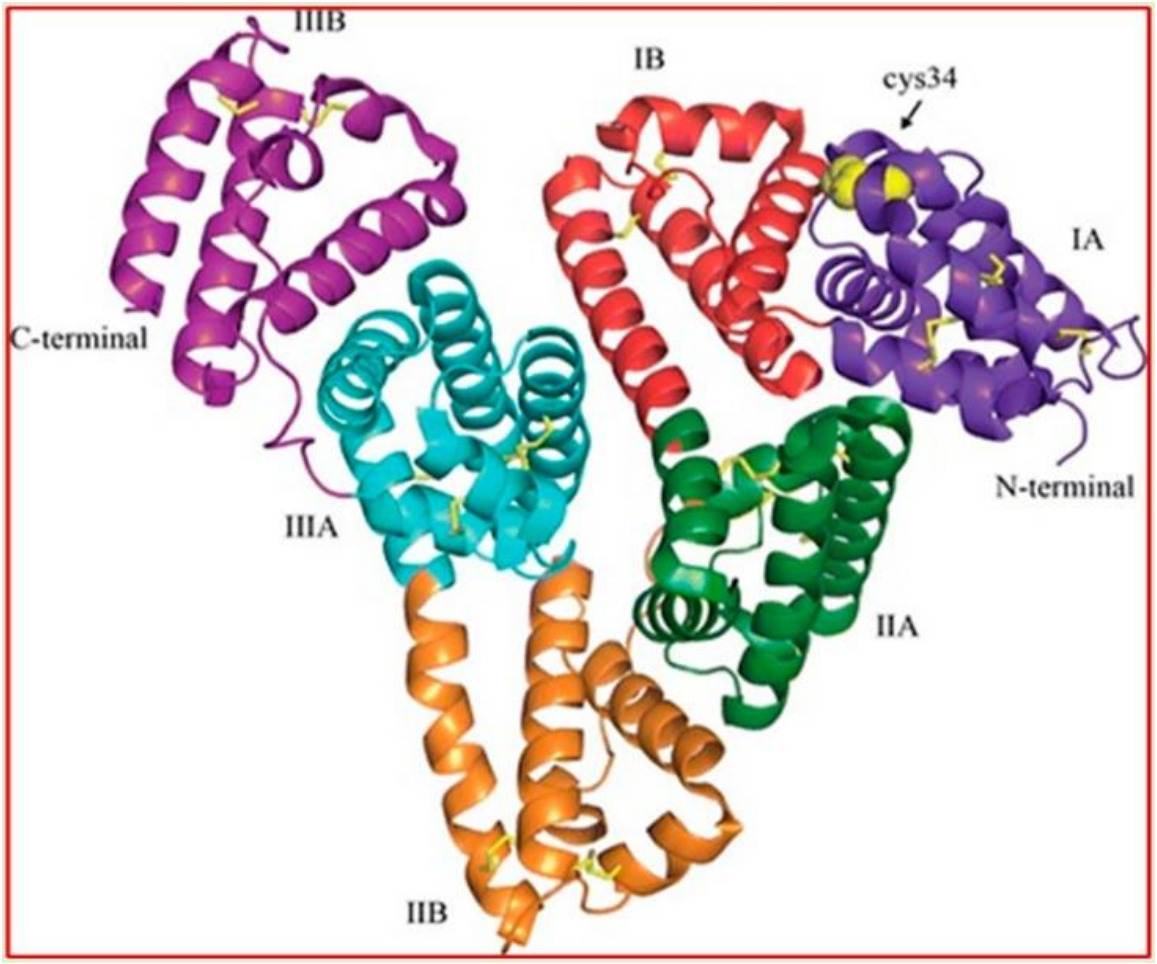

Fig.3. the human serum albumin structure consists of a single polypeptide chain containing 585 amino acids. It forms a heart-shaped protein composed of three homologous domains: domain I spans residues 1 to 197, domain II spans residues 189 to 385, and domain III spans residues 381 to 585. Each domain comprises two subdomains, labeled A and B, which share common structural motifs. These domains are represented in different colors: purple (IA), red (IB), green (IIA), orange (IIB), blue (IIIA), and violet (IIIB). The structure includes yellow sticks indicating disulfide bridges and yellow spheres representing the free cysteine residue at position 34 (Cys34) in domain IA.

Human serum albumin comprises a single chain of 585 amino acids and exhibits a highly flexible secondary structure, consisting predominantly of 67% helical formations. It features 17 disulfide bridges, with six turns acting as connectors between its three homologous domains. (11) Produced by hepatocytes in the liver at a rate of approximately 912 grams per day, human serum albumin is among the most abundant and crucial proteins in blood plasma, with levels typically ranging from 3.5 to 5 grams per deciliter.(12) Despite its abundance, the majority of albumin remains stored in the interstitial space, accounting for up to 60% of its

total amount. Despite having a biological half-life of 19 days, its duration within circulation is limited to approximately 16 to 18 hours. The movement of albumin across capillaries is reversible, allowing it to return to the plasma via the lymphatics to maintain consistent plasma protein concentrations. Its production is regulated by various factors, including insulin, thyroxin, and cortisol levels, as well as conditions such as hypoalbuminemia, which stimulate synthesis, while factors like potassium levels and exposure to excessive osmotic pressure inhibit it.

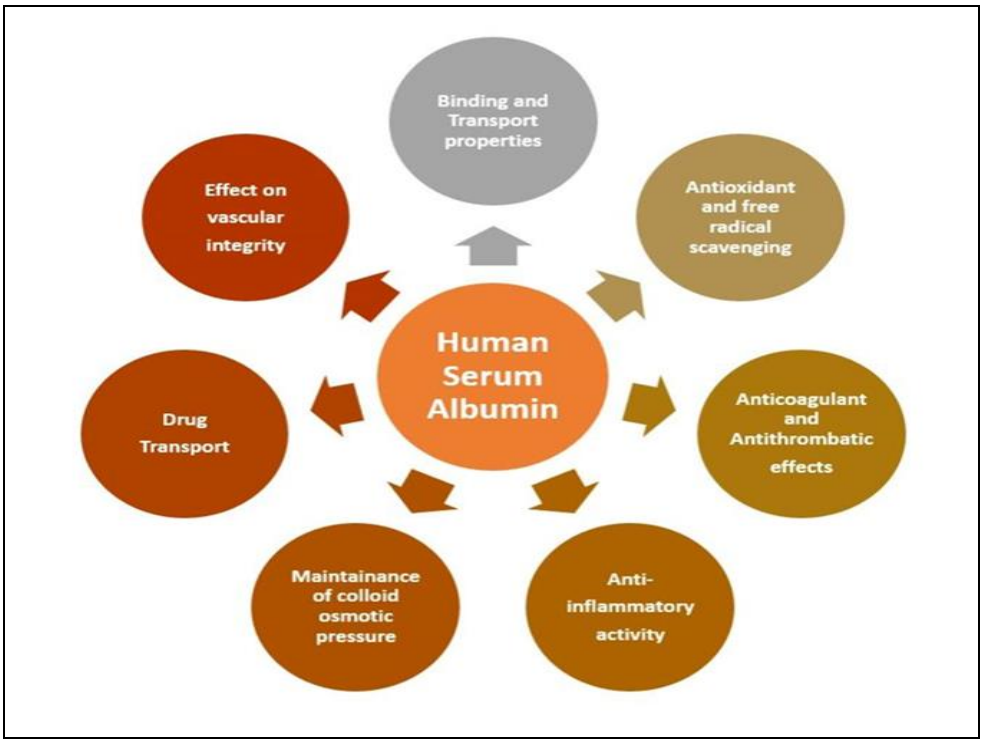

Fig.4 Importance of human serum albumin (30)

Specific antioxidant capacities of native HSA:

Human Serum Albumin (HSA) is a crucial non-glycosylated protein with a molecular weight of 66 kDa (31, 32). Under normal conditions, it is present in plasma at concentrations ranging from 35 to 50 g/l, making up around 60% of the total plasma proteins (33). It boasts a relatively extended half-life of approximately 20 days.

The structural composition of HSA involves a single-chain polypeptide comprising 585 amino acid residues. Notably, its structure consists of roughly 67% alpha-helix and no beta-sheet content (34, 35). Within its makeup, native HSA contains 6 methionines and 35 cysteine residues that participate in the formation of 17 disulfide bonds. Of these, the Cys-34 residue stands out as the sole free cysteine in the entire molecular structure.

HSA showcases distinctive antioxidant properties attributed to its unique structural characteristics. These include its ability to bind to various ligands and its capacity to trap free radicals, which are closely associated with its specific structure (35, 36). These features enable HSA to play a crucial role in antioxidant defense within the body.

HSA antioxidant properties related to ligand-binding capacities:

The antioxidant properties of Human Serum Albumin (HSA) are closely associated with its ability to bind a wide array of molecules, encompassing fatty acids, drugs, hormones, and metal ions (33). Among the various ligands, transition metal ions, primarily copper and iron, play a crucial role in the direct or indirect antioxidant functions of the protein (37).

The foremost site of interaction for Cu (II) ions resides in the initial four amino acids, Asp-Ala-His-Lys (DAHK), located at the N-terminus of HSA (37, 38). Unbound redox-active transition metal ions like Cu (II) and Fe (II) have the potential to be exceedingly pro-oxidant. Via the Fenton reaction, these ions can react with hydrogen peroxide (H2O2), catalyzing the production of highly reactive oxygen species (ROS). This entire sequence is known as the Haber-Weiss reaction, highlighting the significant involvement of iron and copper in human diseases and their role in generating hydroxyl radicals within the body (37, 32). Binding free transition metals to proteins can regulate their reactivity and limit their availability for the Fenton reaction, thus potentially reducing damage caused by hydroxyl radicals generated from the Fenton reaction between iron/copper and H2O2 (38).

Additionally, HSA exhibits affinity for bilirubin, with a high-affinity site (Lys240) for bilirubin within its structure (33). Bilirubin, once bound to HSA, acts as an inhibitor of lipid peroxidation, thereby demonstrating an indirect antioxidant effect of the protein (39). Another aspect of HSA's antioxidant properties is its ability to bind homocysteine, a sulfur-containing amino acid formed during the breakdown of the methionine residue (40).

Although HSA's capability to bind polyunsaturated fatty acids and sterols has been suggested to contribute to its antioxidant properties by averting lipid peroxidation, further research is necessary to validate and document this protective capacity (41, 42). In summary, HSA's antioxidant prowess is notably influenced by its interactions with transition metal ions, bilirubin, homocysteine, and potentially with fatty acids and sterols, suggesting a complex interplay of binding activities crucial for its protective role in combating oxidative stress.

HSA antioxidant properties related to free radical-trapping properties:

In physiological conditions, Human Serum Albumin (HSA) primarily exists in two forms: one-third as disulfides combined with cysteine, homocysteine, or glutathione, and two-thirds in a reduced state with a free thiol at the Cys-34 residue, known as human mercaptalbumin. This mercaptalbumin accounts for 80% of the thiols in plasma, serving as a significant source of reactive free thiol.

The free thiol at Cys-34 acts as a potent scavenger of various reactive oxygen and nitrogen species, such as hydrogen peroxide, peroxynitrite, superoxide, and hypochlorous acid. (36) Under oxidative stress, this thiol can become oxidized, forming sulfenic acid (HSA-SOH), a crucial intermediate in redox reactions by reactive species. The outcome of this oxidation depends on whether the sulfenic acid further oxidizes to sulfinic or sulfonic acids (usually irreversible) or is reduced back to the initial HSA-SH form. Sulfenic acid can also form disulfides through reactions with low-molecular-mass thiols, allowing the return to the reduced form.

HSA's involvement in disulfide formation supports its role as an extracellular redox regulator. Additionally, it potentially aids in protecting cells from oxidative stress and may serve as a source of sulfur-containing amino acids for cellular thiol-containing molecule synthesis, such as glutathione. (37)

Under nitrosative stress, mercaptalbumin can be converted into nitroso-HSA, which can transfer the nitrosonium cation to low-molecular-mass thiols, effectively acting as a major reservoir of nitric oxide.

Both methionine and cysteine residues in HSA contribute significantly to its antioxidant activity, accounting for more than 70% of the free radical-trapping ability in serum. In essence, HSA is crucial in maintaining the plasma's redox state, making it the main extracellular molecule responsible for this regulatory function.

HSA's importance as a carrier in the treatment of various disorders:

1) Tumor : When the lymphatic drainage system malfunctions, a leaky capillary can lead to the accumulation of albumin in malignant or inflamed tissues. To visualize tumor uptake in preclinical mice, the dye Evans Blue, which strongly and rapidly binds to circulating albumin, can be injected. This causes subcutaneously developing tumors to turn blue a few hours after injection. Leveraging the extended half-life of albumin in the body, conjugating

therapeutic peptides or cytokines with albumin is an attractive method to improve their pharmacokinetic profile, serving as an alternative to direct drug targeting. Several clinically examined treatments include a arylhydrazone derivative of doxorubicin (DOXO-EMCH), an albumin-bound nanoparticle of paclitaxel (Abraxane), a methotrexate-albumin conjugate, and an albumin-binding pro-drug of doxorubicin. Abraxane has received approval for treating metastatic breast cancer. (43)

2) Rheumatoid arthritis: Rheumatoid arthritis (RA) is a prevalent, long-term inflammatory condition affecting numerous individuals globally. Uncontrolled RA can lead to joint damage and disability. Methotrexate (MTX) is a medication commonly used to treat both cancer and RA. To enhance its effectiveness and address the lack of selectivity for inflamed tissue, a methotrexate-albumin conjugate (MTX-HSA) was developed. This conjugate directly links MTX to lysine residues of human serum albumin (HSA) to extend its half-life. Studies have demonstrated that MTX-HSA significantly reduces cartilage degradation and invasion of synovial fibroblasts in a humanized model of rheumatoid arthritis.(43,44)

3) Dehydration: Albumin plays a crucial role in addressing hypovolemia, a condition characterized by low blood volume. Its ability to draw interstitial fluid back into the circulation significantly contributes to its effectiveness in managing hypovolemia. This process of shifting fluid helps in restoring the depleted blood volume. Patients who are adequately hydrated tend to derive the most benefit from albumin in such cases, as their overall fluid balance supports the albumin's action in restoring blood volume. (43,45)

4) Burn: Albumin can be recommended for addressing oncotic deficiencies that arise after the initial 24-hour period subsequent to severe burns. It serves to replenish the protein loss commonly experienced in such burn cases. However, while it is utilized for this purpose, there is currently no established ideal or standardized treatment plan that specifies the best regimen involving albumin, electrolytes, and fluid in the early stages of burn treatment. (43)The precise and most effective strategy for using albumin alongside electrolytes and fluids for early burn care remains undetermined within the medical field.(15)

5) Acute Respiratory Distress Syndrome (ARDS): Critically ill individuals, particularly those with severe injuries, may encounter acute respiratory distress syndrome (ARDS). The likelihood of experiencing ARDS rises with age and the severity of the underlying condition, and it often leads to fatal outcomes. Patients afflicted by a condition known as acute respiratory distress syndrome (ARDS) commonly endure persistent shortness of breath and

necessitate ventilator support for breathing.(43) Hypoproteinemia is a characteristic of ARDS and could potentially be linked to the development of interstitial pulmonary edema.

6) Cardiopulmonary Bypass Surgery: A recent meta-analysis concentrated on the occurrence of acute respiratory distress syndrome (ARDS) in critically ill patients or those with severe injuries. The probability of developing ARDS increases with age and the seriousness of the condition, and it can lead to fatal outcomes. People affected by acute respiratory distress syndrome (ARDS) commonly endure persistent difficulty in breathing and often rely on ventilators for respiratory support. This condition is a component of ARDS and might be causally linked to the presence of interstitial pulmonary edema.(43)

7) Hemolytic Disease of the Newborn: Hemolytic Disease of the Newborn (HDN), recognized by various names such as erythroblastosis fetalis, isoimmunization, or blood group incompatibility, occurs when fetal red blood cells (RBCs) lacking an antigen present in the mother enter the maternal circulation through the placenta, leading to antibody formation. The antibodies, upon re-entering the fetal circulation, cause damage to the RBCs. In severe cases of HDN in newborns, albumin may be administered in an attempt to bind and remove unconjugated bilirubin. (43)

8) Diabetes: Treating juvenile diabetes or advanced type 2 diabetes involves replenishing reduced insulin production in the body. Ideally, over a 24-hour period, maintaining and bringing down blood glucose levels to normal is achieved using a longer-acting form of insulin. In a recent approach, insulin is modified by attaching a fatty acid, which binds to one of the fatty acid binding sites among the five or seven sites on the HSA molecule. This modification enhances the availability of insulin. GLP-1-(7–37) is a peptide hormone stimulating insulin production selectively in pancreatic cells by cleaving the proglucagon molecule. However, its effectiveness is limited due to a short half-life of 1.5–2 minutes caused by enzyme breakdown. To address this limitation, GLP-1-(7–37) is modified using a similar technique as Levemir®, where a fatty acid, palmitic acid, is added to the ε-amino position of lysine at the N-terminal position of glutamic acid in the GLP-1 peptide sequence. This modification leads to a new medication, liraglutide (Victoza®), an albumin-binding derivative of GLP-1, with a longer plasma half-life of 11–15 hours following subcutaneous administration. Additionally, it is resistant to degradation by enzymes.(43)

Human serum albumin and cancers:

In recent years, there has been extensive research into the accumulation of Human Serum Albumin (HSA) within the tumor microenvironment (TME). This accumulation is a complex process, driven by a combination of passive and active mechanisms. The TME exhibits increased capillary permeability due to nitric oxide secretion and a lack of efficient lymphatic drainage, which passively facilitates the localization of HSA. (57)

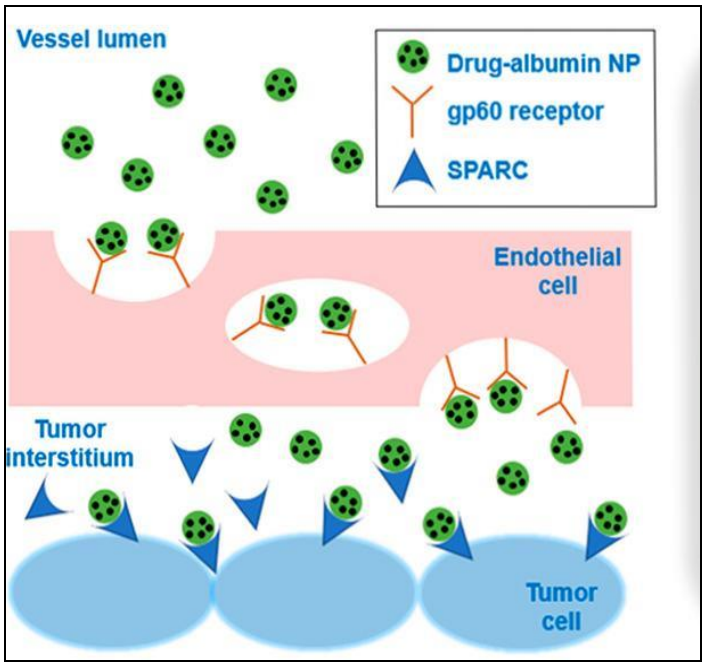

Fig.5 Roles of various HAS receptors gp60 and SPARC

However, an actively orchestrated process also plays a crucial role, involving HSA-specific membrane receptors that are prominently expressed in cancerous cells. These receptors actively recruit HSA to the TME, utilizing it as a source of growth and energy. (57, 58)Notably, among the various HSA receptors, gp60 and SPARC are well-documented for their physiological functions and roles in HSA-based drug delivery, as depicted in fig.5 The significance of employing an appropriate carrier for delivering cytotoxic agents specifically to the TME cannot be overstated. Recent research has shown that using HSA as a nanocarrier, as opposed to gold nanoparticles, proved to be highly effective in targeting the tumor site. This was demonstrated through a biodistribution study that utilized radionucleotide conjugation to the HSA nanocarrier, highlighting its potential in precise and efficient drug delivery to tumor regions. (59)

Nanoparticle Albumin-Bound (NAB)-Technology:

NAB-Technology stands as a frequently utilized technique employing albumin. It is an enhanced form of the previously described emulsion method. NAB-Technology serves as a nanotechnology-based system for delivering drugs, capitalizing on albumin's inherent properties to selectively and effectively transport hydrophobic drugs without the need for toxic solvents. (54)This innovative drug delivery system tackles the limitations associated with the hydrophobic nature of various chemotherapeutic drugs like paclitaxel or docetaxel. It was specifically designed to address the issues presented by the traditional formulations of these drugs. For instance, Taxol (cremophor-ethanol-based paclitaxel) and Taxotere (polysorbate 80-ethanol based docetaxel) displayed adverse effects, including acute toxicity, neuropathy, and hypersensitivity reactions. (55)These reactions are partly linked to the use of cremophor and ethanol in the former formulation and polysorbate 80 and ethanol in the latter. (56)

Premedication becomes essential to avert the harmful side effects of the drug, consequently limiting the maximum tolerated dose. Another factor endorsing the superiority of nanoparticle formulations over alternatives is the leaching of plasticizers from PVC bags due to solubilizing agents like cremophor and ethanol, commonly used in infusion systems. The NAB-technology process, derived from the previously described emulsion-based method, involves a sequential process shown in Figure.5 Here, an oil phase (carrying the drug) is gradually added into an aqueous phase (containing HSA/BSA and pre-saturated with 1% chloroform). The mixture is mildly homogenized at low rpm, forming a preliminary emulsion. The final emulsion is produced through high-pressure homogenization, followed by transferring the mixture to a rotary evaporator, which removes the solvent, resulting in the production of a nanosuspension. This nanosuspension is translucent, consisting of drug-loaded albumin nanoparticles with diameters typically below 200 nm. A 0.22 μm filter is employed to regulate nanoparticle size and sterilize the formulation, eliminating impurities and bacteria. Subsequently, the nanoparticles are lyophilized to obtain solid powders, without requiring the addition of a cryoprotectant. To regenerate the original dispersion, water or saline is added to the solid nanoparticles. (56)

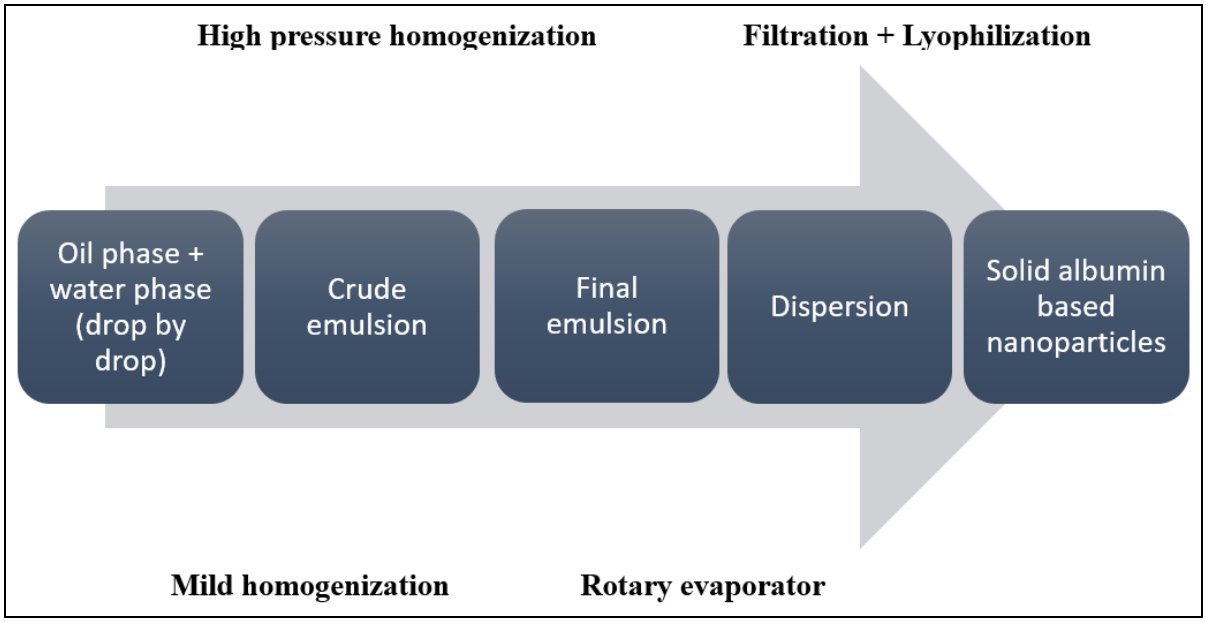

Fig.6 NAB- Technology process

Table 1. Albumin-Based Drug Formulations Currently in Clinical Trials

Formulations	**Type**	**Indications**	**Clinical trials and outcomes**
ABI-007 (Abraxane)	Albumin-based nanoparticle (paclitaxel)	Metastatic breast cancer, Non-small cell lung cancer, Pancreatic cancer	Approved by FDA for breast cancer. Phase III trials combined with other agents. Survival benefits observed.
ABI-008 (Nab-docetaxel)	Albumin-based nanoparticle (docetaxel)	Metastatic breast cancer, Hormone-refractory prostate cancer	Phase I/II trials completed for both indications. Further clinical studies not reported.
Aldoxorubicin (INNO-206)	6-maleimidocaproyl hydrazone prodrug formulation of doxorubicin	Soft tissue sarcomas	Early studies showcased reduced cardio toxicity compared to doxorubicin. Phase I showed safety at 260 mg/m2 dose. Phase II/b trial revealed improved progression-free survival and overall survival in soft tissue sarcoma patients. Phase III trial demonstrated significant time to progression or death compared to standard treatments. Reduced cardiotoxicity compared to

			doxorubicin.
MTX-HSA	Methotrexate	Renal cell carcinoma	Phase II Approved by FDA for renal cell carcinoma
ABI-009 (Nab-rapamycin or Nab - sirolimus)	Albumin based nanoparticle (rapamycin)	Several pulmonary arterial hypertension, advanced sarcoma, advanced malignant PEComa, low or intermediate grade neuroendocrine tumors of the lung or gastroenteropancreatic system.	Phase I and Phase II
NAB-5404 (ABI-011)	Thiocolchicine dimer	Solid tumors and lymphomas	Phase I approved by FDA for tumors

Table 1. Reference (47,48,49,50,51,52)

Future Perspectives:

Albumin has displayed significant potential in both preclinical and clinical studies. Its active internalization in tumors and inflamed tissues is primarily attributed to gp60 and SPARC, although the involvement of gp30 and gp18 and their interactions with albumin nanocarriers require further investigation. Additionally, understanding how the binding of ligands to albumin influences their efficacy is crucial. Furthermore, the methods of albumin preparation and the mechanisms for loading need more comprehensive exploration. In this context, there is a growing need to focus on the development of safe cross-linkers for stabilizing albumin nanoparticles. Notably, tumors have the capacity to capture plasma proteins and utilize their breakdown products to support their growth and development.

Human Serum Albumin (HSA) possesses inherent versatility for interacting with a wide range of molecules, whether they are peptidyl or non-peptidyl in structure. It offers multiple hydrophobic cavities, a single free cysteine, and two termini that can be employed for non-covalent interactions, conjugation, and genetic fusion. These attributes make HSA a versatile platform for binding multiple drugs simultaneously in various combinations, potentially leading to synergistic therapeutic effects. Given its remarkable advantages, as discussed in this review, albumin stands out as an appealing foundation for the development of advanced drug delivery systems in the future.

CONCLUSION:

In conclusion, the utilization of human serum albumin (HSA) as a carrier for drug delivery via albumin nanoparticles offers a promising avenue for treating various disorders. The preparation methods of albumin nanoparticles, such as desolvation, coacervation, and nanoparticle albumin-bound (NAB) technology, provide versatile strategies for encapsulating and delivering therapeutic agents.

The versatility of albumin nanoparticles is evident in their potential application in treating diseases like cancer and rheumatoid arthritis. These nanoparticles, due to their biocompatibility and potential for controlled drug release, hold significant promise in enhancing drug efficacy and minimizing side effects.

The involvement of specific receptors such as gp60 and SPARC in the targeting and uptake of albumin-bound drugs further enhances the precision and efficiency of treatment. Moreover, the ongoing clinical trials showcasing albumin-based formulations underline the growing interest and potential of albumin as a carrier in nano drug delivery, signaling a transition from theoretical concepts to practical application. These trials are essential in validating the safety and efficacy of albumin-based formulations across various medical conditions.

In essence, the multifaceted nature of albumin as a carrier in nano drug delivery, the innovative techniques for nanoparticle preparation, the targeting mechanisms via specific receptors, and the current progress in clinical trials collectively highlight the immense potential and wide-ranging applicability of albumin-based drug delivery systems in revolutionizing the treatment of diverse disorders. These advancements pave the way for a new era in drug delivery strategies, showcasing the promising role of albumin in improving therapeutic outcomes while minimizing adverse effects.

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